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Total Laboratory Automation and Diagnostic Immunology

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"The first rule is that a robot may not allow . . . a human to come to harm."

Isaac Asimov (2)

A Two-Person Conversation in a Fugue State

GATES: What a great era: computers, microchips, browsers, automation, and worldwide windows.
FEYNMAN: Don't forget quantum physics. Don't forget rubber gaskets. Don't forget bongo drums.
GATES: Quantum physics helps us develop computer networks but gaskets and bongo drums? This is difficult, very difficult, maybe even macrodifficult to understand.
FEYNMAN: Inferior rubber gaskets and greed led to the Challenger tragedy.
GATES: What's your point?
FEYNMAN: Untested technology, as sophisticated as it may appear in planning, is still untested. Each system needs to be validated. Human invention and intervention is needed to prime and maintain progress.
GATES: We agree on something. A great idea, from whatever source, is not useful until it is tested and validated. But bongo drums . . .
FEYNMAN: Have some fun along the way.

The number of total laboratory automation (TLA) installations is growing but TLA has only begun to impact diagnostic immunology. I will use the terms integrated laboratory automation, laboratory automation system, and TLA interchangeably in this commentary. TLA is intended to be a system of laboratory instruments under a unified control that requires little or no human intervention at any stage of the process. The process may include drawing blood, reporting the result, and discarding or saving the sample.

Automation is old stuff in clinical laboratories: the speed, quality, and diversity of instruments designed to perform testing on blood and urine samples have continued to improve since the end of World War II. These instruments first mimicked manual methods but later took advantage of newer technologies. First clinical chemistry and then hematology were impacted by these instruments, which allowed laboratories to meet the large increase in testing demand without adding greatly to the number of staff and costs. If anything, the cost per test was reduced. But clinical laboratories remained cottage industries with each section, such as chemistry, microbiology, hematology, and immunology, doing its own thing and having its own management and performance and quality rules. There was little interdisciplinary cooperation (5).

Dr. Masahide Sasaki in Kochi, Japan, in the 1980s created the first and a most dramatic example of an integrated and automated laboratory. Dr. Sasaki used existing analytic instrumentation but rearranged their physical positioning in the laboratory and developed conveyance and robotic systems. He linked instrument stations with conveyor belts and overhead tracks to move samples. Laboratory computers controlled all of the activities. Dr. Sasaki was compelled to develop a highly automated laboratory because he did not have an adequate personnel budget to support a busy facility in a busy health care institution. The Kochi laboratory requires only a fraction of the number of people needed to do a similar number of tests in a typical clinical laboratory in the United States.

Since Dr. Sasaki's innovative beginning, other laboratories have installed total automation systems, usually in cooperation with the manufacturer of such systems. There are currently about two dozen such installations in Japan. Excluding commercial laboratories, there are only a handful of TLA facilities in the United States and perhaps even fewer in Europe (1).

The potential advantages of total automation are clear: decreased personnel and operating costs, less human intervention and fewer laboratory errors, more rapid processing of samples and recording of results, increased safety, better control of the entire process, and decreased need for laboratory space. The disadvantages are somewhat more difficult to understand at this early stage of TLA development. The obvious ones are costs and technology. The start-up costs for laboratory automation are large. In the past, a "payback" period for laboratory equipment of 2 to 3 years was viewed as adequate. The pay-back period for TLA may be 5 to 7 years or more. Administrators are concerned, and should be concerned, about obsolescence over that time frame. The cost problem is related in part to technology. Laboratory equipment manufacturers have each done their own thing in the past. Thus, the computer codes, bar codes, electrical systems and event status descriptors have varied from manufacturer to manufacturer and even from product to product. TLA producers have exhibited the same nonconformist behavior. Much of this individuality stems from the lack of acceptable standards.

Over the past few years, there has been an accelerating effort to develop such standards. In the spring of 1997, the National Committee for Clinical Laboratory Standards (NCCLS) named five subcommittees to tackle the contentious issue of automation standards. The NCCLS is composed of three groups: government, industry, and academia. The organization has a long history of developing standards for the clinical laboratory through a well-tested and laborious consensus process. In this case, the NCCLS asked for and received participation from groups in Japan as well as Europe. The process of developing standards is ongoing and the first documents will soon be released for international review. The overall goal is to allow each site interested in automation to "plug and play," that is, to be able to choose instruments, conveyances, and centrifuges, etc., from a number of different vendors with the assurance that all will match the overall system (4). We are a long way from this goal.

What is the status of automation in the diagnostic immunology laboratory? The composition of assays performed includes both automated assays such as immunoglobulin quantitation by nephelometry and manual tests such as antinuclear antibody (ANA) detection by indirect immunofluorescence. In some sites, diagnostic immunology laboratories also use immunological methods such as in hepatitis or thyroid function determinations. Those tests that are already included on automated

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laboratory instruments will be most easily integrated into a TLA scheme. Indeed, some of the equipment manufacturers have developed instrument modules or platforms connected by technology and/or clinical use. These modules are the next logical stepping-stones for most laboratories as they move towards complete automation.

Tests with automated read-outs, for example, enzyme-linked immunosorbent assays (ELISA), have been semi-automated through the use of robotic arms. Thus, these tests could also be put online with the use of conveyances and robotics. Assays requiring human read-out, for example, ANA detection by indirect immunofluorescence or protein immunofixation, will be the last bastion from TLA. However, technology is encroaching on even these determinations. For example, there is a growing trend to replace the ANA immunofluorescence assay with an ANA ELISA. Capillary electrophoresis and immunosubtraction might replace immunofixation. Many tests are already automated within the diagnostic immunology laboratory. As read-outs become more automated, these tests will also be integrated into a laboratory automation system. The decision to switch will be made on the basis of adequate quality and cost.

The reasons that diagnostic immunology is not more automated relate to the lack of standardized assays and interpretations, the low volume of such tests relative to those in other laboratory sections, and the high risk/benefit ratio of investing in development. Many of the determinations performed in the diagnostic immunology laboratory are not easily automated. These obstacles to automation still exist. The financial risks for reference laboratories that perform a growing portion of diagnostic immunology assays are decreasing, and these companies are more likely to invest in development. Improvements in technology will allow more tests to be more readily automated. There remain two major issues to consider in the movement towards TLA: standardization and validation of assays.

Manufacturers, laboratorians, and regulatory agencies might cooperate to develop standards or they could be mandated by federal or state agencies. Of course, this is true not only for automated assays but also for manual ones. Standardization already is a major concern in the diagnostic immunology laboratory. Automation places emphasis on this problem.

As methods changes, the new automated assays must be validated against the existing ones. This assumes that the existing tests already have a sound scientific basis in regard to sensitivity, specificity, predictive values, and clinical utility. We have already seen failures by industry, laboratories, and government in releasing newer versions of existing measurements without adequate documentation. Governmental regulations are not stringent and fall far short of what is required to ensure that new pharmaceutical products are properly validated (3). Yet, drug use may be dependent on the result of an inadequately validated assay! Unless there are legal or regulatory changes, it will be incumbent on laboratories to validate each new method, deciding what is a "positive" test result versus a "negative" test result and the clinical relevance of the test result. Otherwise, total laboratory automation will automatically produce many inferior and misleading results. The manufacturers have a major, probably the predominant, responsibility in this area.

TLA will be integrated into the diagnostic immunology laboratory in some settings. These laboratories will eventually produce results more efficiently and more economically. They will need fewer medical technologists but more computer specialists and engineers. The total number of employees will be greatly reduced. The development of TLA will require vigilance by an informed and articulate group of professionals who will accept the challenge of focusing on the public well-being.

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